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First things first: Protecting children with asthma from infection with influenza

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Currently in the U.S., approximately 7 million children (9.4%) have asthma (1), making it the most prevalent serious chronic illness among U.S. children. Clinically, the association of viral respiratory infections and asthma exacerbations has been understood for decades. More recently, infections with particular viruses have been identified as being particularly risky: respiratory syncytial virus, rhinovirus, and influenza virus are notable examples. In the spring of 2009, a new influenza virus (A(H1N1)pdm09 [2009 H1N1]) with pandemic potential was isolated from patients in the U.S. and around the world (2). Early data indicated that certain comorbid medical conditions increased the risk for hospitalization and intensive care unit admission (3). Persons with asthma appeared to bear a disproportionate risk, and local and state health departments along with Centers for Disease Control and Prevention (CDC) developed and disseminated guidance early in the outbreak for persons with asthma and their health care providers. Early diagnosis and use of antiviral medication, along with public health practices like self-distancing and hand-washing, were emphasized. Persons with comorbid conditions (including asthma) were prioritized to receive vaccine once it became available. These recommendations, however, were more re-iterations of existing practices and policies rather than *de novo* interventions. As was consistent with previous recommendations, vaccination of persons with asthma was to prevent influenza because of the risk of increased disease severity, rather than increased risk of becoming infected with influenza virus. Analysis of existing data did not, at that point in time, support (nor refute) an increased risk of infection among persons with asthma.

In this issue of *American Journal of Respiratory and Critical Care Medicine*, Kloepfer and co-authors demonstrated an increased risk of infection with 2009 H1N1 influenza virus among persons with asthma. The opportunity to collect the data to demonstrate this finding was serendipitous: the authors had a well-planned, ongoing study of viral respiratory infection and asthma at the time the fall wave of the 2009 outbreak arrived in their locale.

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The study protocol was modified to include the new influenza virus, permitting the collection of the data needed to show not only increased risk of worse clinical outcomes, but of influenza infection itself. This finding strengthens the recommendations of the Advisory Committee on Immunization Practices (ACIP), the National Asthma Education and Prevention Program (NAEPP), and CDC for routine influenza vaccination among persons with asthma.

The authors were not able to demonstrate the cause of the increased risk of infections; hypotheses include altered immune status related to asthma, lessened local cell-mediated immune response from inhaled corticosteroids (which, however, remain the bedrock of most asthma care, and good asthma control going into cold & flu season is essential for this population), co-infections or other comorbidities, among other possibilities. Why had data from previous studies not been able to demonstrate this finding? Most previous data on influenza vaccination is obtained by retrospective report, such as in the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS). Of course, a prospective study that involved withholding vaccination would be unethical. However, in 2009 a novel viral strain (2009 H1N1) was identified after trivalent (seasonal) production started and required 2009 H1N1 monovalent vaccine as an additional vaccine to that year's 2009–10 trivalent (seasonal) vaccine. This natural experiment, in conjunction with the authors' existing prospective study, allowed the question of increased risk of infection to be answered.

Unfortunately, influenza vaccination coverage among persons with asthma remains low—under 40% overall, except in persons aged 65 or over—each influenza season, including during the 2009 pandemic flu episode that began in 2009 (1). Although an increased number of health-care visits is associated with increased likelihood of vaccination, the same data more starkly demonstrate the missed opportunities for vaccination: even among persons with asthma who had ≥ 10 health-care visits during the influenza vaccination season, only 50% received the seasonal vaccination in 2005–06 (4). A similar study using the BRFSS dataset for the 2006–07 found that among adults with asthma, only 39.9% received the influenza vaccine. People with asthma who had an increased likelihood of vaccination were aged 50–64 years, female, non-Hispanic white, and had diabetes, activity limitations, medical insurance, a regular medical care provider, routine checkup in the previous year, and formerly smoked or never smoked. Additionally, the 2009 H1N1 vaccination coverage among adults with asthma was only 25.5% (5).

Although the authors in the current study answer an important, previously unanswered question, the essential question remains: why are persons with asthma not receiving flu shots? Even more broadly, why are persons with asthma not on treatment programs consistent with the NAEPP EPR-3 guidelines? When the most recent version of the guidelines was published in 2007, the NAEPP provided the following guidance: *The Expert Panel recommends that clinicians consider inactivated influenza vaccination for patients who have asthma. It is safe to administer in children over 6 months and adults who have asthma (Evidence A), and the Advisory Committee on Immunization Practices of the CDC recommends the vaccine for persons who have asthma because they may be at increased risk for complications from influenza* (6). To be consistent with the ACIP, these guidelines

should be strengthened to *recommend* influenza vaccination for all patients with asthma because they *are* at increased risk for complications from asthma. Nevertheless, recommendations for influenza vaccine and other key recommendations, such as "*inhaled corticosteroids are the most effective anti-inflammatory medications for long-term management of persistent asthma*," and "*all people with asthma should receive a written Asthma Action Plan*," have similarly low uptake among patients with asthma.

The concept of translational research—moving bench science to bedside—must go hand-in-hand with translational public health, i.e., moving evidence-based guidelines into routine practice. Kloepfer and co-authors add to the evidence supporting influenza vaccination of children with asthma; we now need to routinely provide influenza vaccination to our patients with asthma. Persons with asthma are recommended to have routine follow-up visits at 1 to 6 month intervals to ensure that control of asthma is maintained. These follow-up physician visits can provide important opportunities for physicians to vaccinate persons with asthma or to remind them that they need to get an influenza vaccination. Additionally, offering influenza vaccination in the emergency room (ER) to those with asthma would be appropriate. Sometimes that is the only place these patients are seen.

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